REMARKS

Claims 2, 3, 5-7, 9-11, 14-17, 19, and 22-33 are pending in the present application. No amendments are being made in this paper and thus, no new matter is added.

The October 7, 2010 Final Office Action

Rejections under 35 U.S.C. §103

Claims 2-3, 5-6, 9-11, 19, 14-16, 22-30, and 32-33 remain rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Chamberlain et al. (reference 19 of IDS filed 3/10/04, "Chamberlain") in view of Geistlich et al. (reference 5 of IDS filed 3/10/04, US 5,837,278, "'278 patent") and further in view of Geistlich et al. (reference 1 of IDS filed 3/10/04, US 6,221,109, "'109 patent").

The Office Action repeated the previous assertions concerning the cited references. In that regard, according to the Office Action, Chamberlain teaches collagen tubes for nerve regeneration that can be filled with a type I collagen/chondroitin-6-sulfate material (collagen and a glycosaminoglycan copolymer known as collagen-GAG (CG) copolymer) that acts as a nerve growth stimulant. The Office Action further stated that said tube is 20mm long with an internal diameter of 1.5mm (directing attention to the abstract, pages 1394-1395, and Figure 1). According to the Office Action, the collagen fiber filling material is longitudinally oriented with respect to the tube (page 1395) and laminin can be a promoter of nerve regeneration inside the tube (page 1394). The Office Action stated that Chamberlain discloses methods of placing nerves inside the tubes for regeneration (abstract and pages 1395-1396). (The Office Action

noted that Myron Spector is a co-author of the Chamberlain et al. reference, and is also a co-inventor of the instant Application).

The Office Action acknowledged that Chamberlain does not teach a tube formed from a single sheet of collagen prepared from peritoneal membrane that has an outer smooth barrier surface and a soft fibrous surface opposite the smooth barrier surface. The Office Action asserted that the '278 patent discloses a single sheet of a resorbable sidewall material consisting essentially of a single layer collagen sheet material having a compact, smooth outer barrier surface so as to inhibit cell adhesion thereon and act as a barrier to prevent passage of cells therethrough, and this sheet material further has a fibrous inner surface opposite the smooth barrier surface (column 1, line 51 to column 2, line 6) derived from collagen membrane peritoneal tissue (column 2, lines 52-60). The Office Action noted that this single layer collagen sheet material is identified as Bio-Gide® by the instant specification (page 3, paragraphs 0017 and 0018), and is the same material disclosed in the '278 patent. The Office Action has taken the position that Bio-Gide® inherently meets all the claim limitations of claims 2-3, 11, 14-15, 23-28, and 33. (The Office Action noted that Peter Geistlich is a co-inventor of the '278 patent and is a co-inventor of the instant Application). The Office Action acknowledged that the '278 patent does not disclose that Bio-Gide® is suitable for use with nerve tissue. The Office Action further stated that the '109 patent (second Geistlich et al. reference) teaches that Bio-Gide® can be wrapped around the spinal cord and dura sheath in order to protect both from injury during spinal surgeries and also to protect the spinal area from ingrowth of connective tissue and undesired cells which might interfere with proper healing. (The Office Action directed attention to column 1, lines 9-1 8 and column 1, line 54 to column 2, line 9 and to Figures 1 and 3).

On the basis of the above, the Office Action has concluded that it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use the collagen tubes of Chamberlain with the Bio-Gide® of the prior art patents because, in the opinion expressed in the Office Action, while Chamberlain teaches that collagen tubes have multiple advantages over silicone tubes, "the required characteristics of a nerve guide remain to be fully delineated" (citing page 1401). The Office Action further stated that while porous collagen tubes permit diffusion of nutrients and growth-promoting factors from the external environment to the injured nerves in order to promote nerve regeneration (an observation the Office Action indicated is supported by two studies according to Chamberlain), if the tube is too porous, important wound-derived neurotrophic factors may be allowed to exit the injury site prematurely through the tube. The Office Action stated that Chamberlain reports that his own study has shown that the most favorable results were obtained with a non-porous collagen tube filled with a CG copolymer because said tube facilitated the retention of the endogenous neurotrophic factors in the nerve injury gap site while allowing for the infiltration of smaller molecular weight nutrients through the tube. The Office Action asserted that Chamberlain concludes "additional experimentation with porous and non-porous collagen tubes that differ in permeability may be used to address this issue" (page 1402), which, in the opinion expressed in the Office Action, is an explicit direct suggestion by the primary reference to substitute the finite group of other known collagen tubes for the known and motivating purpose of improving the therapeutic results. The Office Action asserted that a clear nexus thus forms between the '109 patent which teaches Bio-Gide® collagen membranes formed into a tube around nerve tissue (spinal cord) (Figure 1 of the '109 patent) with the smooth barrier face facing the exterior to protect the surgical site from ingrowth of unwanted cells (column 3, lines 5-10) while the fibrous

face opposite the smooth face faces inward, allowing cell growth thereon (column 2, lines 1-4 and Figure 3), and the Chamberlain reference which discloses that "in the tubulization method of treating nerve gaps, tubes can enhance regeneration by serving to (1) contain matrices that have been found to enhance the regenerative process, perhaps by providing a scaffold for 'contact guidance' . . . (2) prevent ingrowth of adjacent tissue into the gap, and thereby prevent fibrocollagenous scar formation in the gap" (directing attention to pages 1399-1400). The Office Action asserted that both the '109 patent and Chamberlain share a nexus to combine Bio-Gide® with the nerve regeneration methods of Chamberlain because, in the opinion expressed in the Office Action, Bio-Gide® has an interior surface that allows cell growth thereon ('109 patent) which the Office Action asserted is very similar to providing a scaffold for 'contact guidance' (Chamberlain). The Office Action further stated that Bio-Gide® has an exterior surface preventing ingrowth of unwanted cells which, according to the Office Action, is exactly equivalent to preventing ingrowth of tissue that would form scars in the nerve gap and inhibit nerve regeneration (directing attention to Chamberlain). The Office Action asserted that the '278 patent makes the connection between Chamberlain's suggestion to try other collagen tube materials in order to make and use a better nerve regeneration tube with the Bio-Gide® of the '109 patent even stronger because, in the opinion expressed in the Office Action, the '278 patent reiterates the advantages of Bio-Gide® in relation to its desired property of excluding unwanted cells and simultaneously providing a fibrous surface that improves the ability of wanted cells to grow. (The Office Action directed attention to claims 1 and 18 of the '278 patent).

The Office Action further asserted that the '278 patent also teaches the advantages of making and using Bio-Gide® with chondroitin sulfate (directing attention to claim 11) and glycosaminoglycan (directing attention to claims 9, 12, and 24), which, according to the Office

action also is disclosed by Chamberlain for improving his collagen tubes (the Office Action citing pages 1395 and 1402). In the opinion expressed in the Office Action, given the combined teachings of the three references, it would have been *prima facie* obvious to substitute the collagen of the nerve regeneration tubes of Chamberlain with the Bio-Gide® collagen of the patents because of the known advantageous properties of the two different surfaces of Bio-Gide® in order to make and use an improved collagen nerve regeneration tube, which the Office Action asserted is explicitly and directly suggested by Chamberlain. The Office Action finally concluded that because, in the opinion expressed in the Office Action,

> all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention because the nexus between all the references makes the substitution of a known similar product (Bio-Gide® collagen for collagen type I) from a finite list of known collagens for a known similar purpose (nerve tissue healing) in order to produce a known similar result (improved tissue healing by improved interior cell growth while excluding unwanted exterior cells) with a reasonable expectation of success is also *prima facie* obvious. See *KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727(US. 2007).*"

The Office Action also included further comments in response to the arguments presented in Applicants' October 1, 2009 paper. Specifically, the Office Action asserted that Applicants argue that the instant invention is distinguished from the prior art by having a soft fibrous inner surface and that subsequent research and analysis indicates that the thickness of the fibrous scar which forms along the inner surface of the tube is related to the topography of the surface. (The Office Action refers to page 14 of Applicants' October 1, 2009 response). The Office Action goes on to state that "[t]he fact that applicant may have recognized another advantage which

would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious," directing attention to Ex parte Obiaya, 227 USPQ 58, 60 (B. Pat. App. & Inter. 1985).

The Office Action further asserted that Applicants were attacking references individually and stated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In purporting to be responding to "Applicant's argument that there is no reference to nerve regeneration or any use in connection with nerves with regards to Geistlich '278," the Office Action asserted that "this is an argument not in combination with the other references, and . . . a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." The Office Action further stated that if the prior art structure is capable of performing the intended use, then it meets the limitations of the claim. The Office Action further stated that "Applicant's arguments drawn to unexpected results concerning scar formation . . . are unpersuasive because the results are not unexpected because, as Chamberlain noted already of record, his tube can 'prevent ingrowth of adjacent tissue into the gap, and thereby prevent fibrocollagenous scar formation in the gap.'" The Office Action continued, re-asserting from the original rejection of record that the '109 patent teaches that Bio-Gide® can be wrapped around the spinal cord and dura sheath in order to protect both from injury during spinal surgeries and also to protect the spinal area from ingrowth of connective tissue and undesired cells which might interfere with proper healing. The Office Action finally stated that "[s]imilarly, the increased number of axons seen in the instant invention was a predictable result as indicated in the previous Office Action

concerning a favorable interior environment of the tube in combination with excluding the deleterious outside environment."

The Office Action further states that Applicant argues that Integra tubes do not have a soft fibrous inner surface and even goes so far as to assert that "[t]his is a straw man argument because the Examiner's position is clear that the combination of the references leads the ordinary artisan to use Bio-Gide® to make the tube, not Integra." The Office Action then makes the astonishing statement that "[t]he motivation for substituting Bio-Gide® for Integra to form the tube is exactly the improved performance that results; the improved performance is not unexpected." (See Office Action page 8).

In response, Applicants respectfully traverse the rejection. The present claims are directed to a nerve regeneration tube for reconnecting nerve ends, a method for producing such a tube, and a method of reconnecting nerve ends utilizing such a tube. The tube is resorbable and has a resorbable sidewall formed with collagen sheet material having a compact smooth outer barrier surface, and a soft fibrous inner surface opposite the smooth barrier surface. The tube has a compact smooth outer barrier surface formed with the compact smooth outer barrier surface of the collagen sheet material so as to inhibit cell adhesion thereon and to act as a barrier to prevent passage of cells therethrough. The tube further has a soft fibrous inner surface for promoting nerve growth, the soft fibrous inner surface of the tube being formed with the soft fibrous inner surface of the collagen sheet material. The tube has an inner diameter of about 0.5 – 5 mm, and has opposite tube ends, within which tube ends, during use, are nerve ends for reconnection of the nerve ends, wherein the nerve regeneration tube avoids formation of scar tissue which impairs nerve healing. Thus, the present claims refer to a soft fibrous inner surface opposite the compact smooth outer barrier surface to facilitate nerve regeneration.

First, Applicants again note the Office Action's specific acknowledgment that "Chamberlain does not teach a tube formed from a single sheet of collagen prepared from peritoneal membrane that has an outer smooth barrier surface *and a soft fibrous surface opposite the smooth barrier surface*." (Emphasis added). This is a significant fact in that, as Applicants have noted before, the present invention has unexpectedly advantageous properties over tubes not having this feature, including, specifically, the type of tube referred to in the cited Chamberlain reference. In that regard, Applicants again refer to the Declaration of Dr. Myron Spector and accompanying data and remarks first submitted in the papers filed October 22, 2007 and discussed subsequently in the previously filed papers. Applicants note that the Declaration does indeed provide evidence of unexpected results over the presently cited prior art for reasons similar to those which were found persuasive in overcoming the rejections over previously cited art. In that regard, Applicants assert that the Office has failed to evaluate the proffered evidence in the manner required under Office policy.

As noted earlier, Dr. Spector is one of the inventors in the above-referenced application and is a renowned expert in the field. Dr. Spector has been a Professor of Orthopedic Surgery at Harvard Medical School since 1993, and has conducted research on nerve regeneration tubes for over a decade. As indicated in Dr. Spector's Declaration, the *surface configuration of tubes defined by the present claims provides such tubes with unexpected properties which could not have been predicted based upon the prior art.* In previous papers, Applicants have detailed Dr. Spector's extensive background and history, particularly as it relates to nerve regeneration tubes. As noted, particular studies in which Dr. Spector has participated involved comparisons between silicone tubes and tubes made of collagen, which collagen tubes were obtained from Integra Life Sciences (Integra), Plainsboro, NJ, and are fabricated by freeze-drying Type I microfibrillar

collagen from bovine tendon. The presently cited Chamberlain paper *also* refers to the Integra bovine tendon collagen type tubes (see, e.g., page 1395, column 1). The Integra collagen tubes are formed by collagen slurry injection over glass rods, and do not have a soft fibrous inner surface (as the Office Action has acknowledged). Thus, the Integra collagen tubes do not share the same or similar surface topography as those of the claimed invention. The Declaration evidence previously provided revealed that the claimed invention exhibits unexpected properties over this very type of tube (i.e., the Integra collagen tube). The studies referred to in Exhibits B and C attached to Dr. Spector's Declaration reveal that the Integra (i.e., Chamberlain) tubes had some advantages over silicone tubes. However, the further evidence included with the Declaration revealed that the present invention has unexpected advantages over the Integra (Chamberlain) tubes, which do not share the surface topography of the claimed invention, a feature that has proven to be highly significant. Thus, the Integra tubes had advantages over the silicone tubes, but the tubes of the present invention are surprisingly better than the Integra tubes, the same tubes referred to in the cited Chamberlain reference.

In that regard, attached to Dr. Spector's Declaration as Exhibit D was a summary of a study that Dr. Spector was involved in, and which was presented at the 2007 Society for Biomaterials meeting. The Exhibit D study compares results achieved in five groups of animals (Groups I-V) in a rat spinal cord model for nerve regeneration. The study included testing of the collagen tubes (Groups III and IV) which Dr. Spector and his co-workers fabricated by freeze drying Type I microfibrillar collagen from bovine tendon from Integra, after slurry injection of the collagen over a glass rod mandrel. As noted, these Integra tubes do not have a soft fibrous inner surface, and are of the type referred to in Chamberlain.

As indicated in Dr. Spector's Declaration, the Exhibit D study included testing of BioGide® collagen membrane (Group V) from Geistlich Biomaterials, Wolhusen, Switzerland. This BioGide® collagen membrane material corresponds exactly to the BioGide® collagen sheet material exemplified in the present application and usable in accordance with the present claims. The BioGide® membrane sheet material utilized in Group V of the Exhibit D study has a compact smooth outer barrier surface and a soft fibrous inner surface. In Group V of the Exhibit D study, the tube was formed by wrapping BioGide® membrane sheet material around stump ends of severed spinal nerves, so as to form a nerve regeneration tube as set forth in the present claims, with the soft fibrous surface oriented inwardly toward the severed nerve tissue to form the inner surface of the tube.

As also indicated in Dr. Spector's Declaration, in the Exhibit D study, the Group V animals with tubes formed of Geistlich BioGide® membrane material having a smooth outer surface and a soft fibrous inner surface (i.e., tubes in accordance with the present invention), unpredictably had the highest number of axons in the center of the nerve defect. (See, Figure 1 in Exhibit D).

As further indicated in Dr. Spector's Declaration, in the Exhibit D study, the only difference between the Group V animals and the Group IV animals was the structure of the tubular material surrounding the severed nerve tissue. The "dorsal barrier" mentioned in the Exhibit D study refers to a collagen membrane draped over the implant site to assist in preventing overlying tissue (e.g., muscle) from collapsing into the nerve defect.

As indicated in Dr. Spector's Declaration, taking into consideration the differences in the tube structure alone, between the Group V and Group IV animals, persons of ordinary skill in the art could not have predicted that the presently claimed invention, utilizing the collagen

membrane material of Geistlich et al. U.S. Patent No. 5,837,278 (Group V), could result in the unexpectedly highest number of center nerve axons among the test animals, as compared to collagen tubes without a soft fibrous inner surface (the Group IV tubes, i.e., the Integra tubes, the very type referred to in the presently cited Chamberlain reference).

Moreover, as indicated in Dr. Spector's Declaration, with reference to Exhibit E attached thereto, Fig. 1 thereof shows a cross-section through the BioGide® collagen membrane material with the compact smooth barrier side at the top, and the soft fibrous side at the bottom. As shown in Fig. 2 of Exhibit E, entubulation of a gap in a rat nerve (spinal cord) with BioGide® demonstrated the absence of a thick fibrous scar on the inner surface of the tube, and demonstrated the ingrowth of cells and tissue into the soft fibrous surface. Based on the prior art, persons of ordinary skill in the art could not have predicted the absence of a thick fibrous scar on the inner surface of a tube according to the present invention, in conjunction with ingrowth of cells and tissues into the soft fibrous inner surface of the tube.

Applicants therefore have provided evidence and declaration testimony showing unexpected results, which evidence, if properly considered, should be sufficient to overcome the obviousness rejection raised by the Office Action. It is Applicants' belief, however, that the Office has failed to fully and properly consider the evidence or adequately understand that Applicants' burden has been met.

First, Applicants respectfully direct attention to MPEP §716.02(a)(III), which recites that "[p]resence of a property not possessed by the prior art is evidence of nonobviousness." In that regard, as provided above, Applicants have shown at least two properties not possessed by the prior art.

Moreover, it appears that the Office continues to confuse Applicants' evidence of unexpected results over the Chamberlain tubes with "an attack on references individually." It is true that Applicants have presented data that show unexpected results over the teachings of Chamberlain. In doing so, Applicants respectfully remind the Office that "[a]pplicant is not required to compare the claimed invention with subject matter that does not exist in the prior art." (See MPEP §716.02(e)). In other words, the Applicants cannot be required to show unexpected results over a combination of references, but rather only over something already in the art, i.e., a single art reference. By simply reiterating the combination of cited reference teachings, what the Office Action *at best* can be said to have done is compared the Applicants' results not with existing prior art, but with a nerve regeneration tube that only results from the Office Action's suggested combination of teachings. Such an analysis is simply not proper, as the above noted section of the MPEP clearly indicates, when it also states (citing *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966)):

> Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 "would be requiring comparison of the results of the invention with the results of the invention." 357 F.2d at 422, 148 USPQ at 714. (MPEP §716.02(e)).

Applicants have provided substantial evidence of unexpected results over the Chamberlain reference's teachings, which reference appears to be the closest prior art because it is the only cited reference that can be said to involve a nerve regeneration tube. In any event, however, even if the '278 patent or the '109 patent were considered the closest art, the evidence provided still reflects unexpected advantages.

As noted in Dr. Spector's Declaration, the Geistlich '278 patent discloses a resorbable collagen membrane which is surgically inserted around the periphery of a wound cavity to

facilitate, e.g., bone regeneration. There is no reference to nerve regeneration or any use in connection with nerves, nor is there any reference to formation of tubes for any purpose. Therefore, any results relating to nerve regeneration, especially the results presented in the Declaration, would be unexpected over the teachings of the '278 patent.

The '109 patent is directed to use of collagen membranes to protect the spine after vertebral surgery. This is on an astronomically larger scale than the present invention, and is totally unrelated to the present invention. As set forth in the present application, the nerve regeneration tubes of the present invention are for reconnecting tiny nerves by inserting nerve ends in opposite ends of the inventive regeneration tubes. The claims reflect this manifest difference, by specifying that the nerve regeneration tube has an inner diameter of about 0.5-5mm.

The distinction between the presently claimed invention and the Geistlich et al. '109 patent further is made clear by the claims' recitation that the nerve regeneration tube is for reconnecting nerve ends, and further specifying that the nerve regeneration tube has opposite ends into which ends of nerves are inserted for reconnection and regeneration of the nerves.

As noted above, the Geistlich et al. '109 patent utilizes a collagen membrane to protect a patient's spine following vertebral surgery. There is no hint or even a remote suggestion in the Geistlich et al. '109 patent of a nerve regeneration tube for reconnecting nerve ends, the tube having opposite ends into which ends of nerves are inserted for reconnection and regeneration of the nerves, with the tube having an inner diameter of about 0.5-5mm. Furthermore, Applicants note specifically the Office Action's assertion in connection with the teachings of the '109 patent, that if a structure is capable of performing the intended use of the invention, it meets the limitations of the claims. It is not clear to Applicants, however, how the '109 device, which has

not been adapted structurally for use in nerve regeneration, could perform the intended use of the claimed invention, as the Office Action contends.

In summarizing, therefore, while the Office Action continues to reiterate its previous positions, it still has not even attempted to address the core issue here, and has presented no comments whatsoever on the requirements set forth in the portions of the MPEP cited above by Applicants (relating to Applicant's burden in overcoming an obviousness rejection with evidence of unexpected results). Again, the Office simply has failed to apply the evidence in a manner that is consistent with the law and with Office policy. The Office Action in fact displays a fundamental misunderstanding of how sworn declaration evidence is to be considered, as well as a similarly fundamental misunderstanding of how evidence of unexpected results are to be assessed in relation to the cited art. The Office has not offered sufficient technical reasoning or other rationale in the face of the declaration evidence as to why the extent of axon growth in the center of the nerve defect or the absence of a thick fibrous scar on the inner surface of the inventive tube would have been expected by one of only ordinary skill, based on the art.

The Office Action even has astonishingly stated that "[t]he motivation for substituting Bio-Gide® for Integra to form the tube is exactly the improved performance that results; the improved performance is not unexpected." This reasoning is simply illogical. A result cannot possibly serve as its own motivation to achieve that result. At best, this statement represents the very essence of hindsight and cannot form the basis of, nor provide support for, an obviousness rejection.

Moreover, the Office continues to assert that Applicants have failed to provide unexpected results over the art because the elements the Office has combined from the various references would lead to the results achieved in the invention. This is a fatally flawed analysis as

it sets an impossible burden for an Applicant to meet, which is precisely why the MPEP, as noted above, makes clear that the Office is not permitted to engage in such an analysis.

The Office Action even accuses the Applicants of employing a straw man argument in its approach. This is simply not the case. Applicants have provided *exactly* what is required of them to overcome the obviousness rejection, by demonstrating, through evidence provided in a sworn declaration, that the invention achieves surprising and unexpected results over the art, not over a fictional combination of teachings assembled by the Office, which combination does not exist in the art. Again, Applicants respectfully direct attention to the sections of the MPEP cited herein which make abundantly clear that unexpected results are to be compared to something that actually exists in the art, not something that exists only through a combination of teachings pulled from various references. Consistent with this policy, Applicants have compared results of the invention with individual art references - that is, with tubes that actually exist in the art. This is not a straw man approach, but rather the only approach that can be followed that is consistent with the law and Office policy.

Applicants again, therefore, respectfully urge the Office to consider both the substance of the evidence provided and the manner in which this evidence is required to be evaluated under Office policy and the law. Applicants therefore also respectfully request reconsideration and withdrawal of the obviousness rejection based on Chamberlain, Geistlich '278 and Geistlich '109.

Claims 2-3, 5-6, 9-11, 19, 14-17, 22-30 and 32-33 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Chamberlain, the '278 patent, and the '109 patent as applied to claims 2-3, 5-6, 9-11, 19, 14-16, 22-30, and 32-33 above, and further in view of Fearnot et al.

(US 6,358,284, "Fearnot"). The Office Action acknowledged that Chamberlain, the '278 patent, and the '109 patent do not teach a step of joining two opposite side edges of a collagen sheet material together to form a tube. According to the Office Action, Fearnot does teach a process for producing an implantable graft construct from a sheet of a highly purified form of an implantable tela submucosa collagen matrix (column 6, lines 45-65) formed in the shape of a tube having a seam extending longitudinally along the length of the graft wherein the seam has been sealed to resist movement of fluids from the lumen through the seam to the exterior of the tube (column 3, lines 32-38). The Office Action stated that the tubular prosthesis is envisioned for use with nervous tissue (column 2, lines 63-64). In the opinion expressed in the Office Action, it therefore would have been obvious to one of ordinary skill in the art at the time of the invention to make an implantable graft construct from a sheet of Bio-Gide® in the shape of a tube having a seam extending longitudinally along the length of the graft wherein the seam has been sealed to resist movement of fluids from the lumen through the seam to the exterior of the tube because of the desire to prevent wound-derived neurotrophic factors from leaking out, which the Office Action asserted is suggested by Chamberlain.

The Office Action indicated that Applicant's arguments filed August 5, 2010 have been fully considered but were not persuasive to the Office "because Fearnot is not needed to overcome the deficiencies of the previous rejection."

In response, Applicants respectfully traverse the rejection. Applicants first refer to the comments presented above in connection with the obviousness rejection based on Chamberlain, the '278 patent and the '109 patent. The further cited Fearnot reference does nothing to overcome the nonobviousness of the claims based on the unexpected results noted above, nor

does it provide any other reason to suggest the claims are obvious over the presently cited art. The fact that the Office asserts that the Fearnot reference was not needed to overcome the deficiencies of the previous rejection is irrelevant. It was used in a rejection in combination with other art, the combination of which does not, for the reasons provided in the previous rejection, render obvious the present claims. For at least this reason, Applicants respectfully request reconsideration and withdrawal of the above obviousness rejection.

Claims 2-3, 5-7, 9-1 1, 19, 14-16, and 22-33 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Chamberlain, the '278 patent, and the '109 patent as applied to claims 2-3, 5-6, 9-11, 14-16, 19, 22-30, and 32-33 above, and further in view of Humes (US 5,429,938, already of record).

The Office Action acknowledged that Chamberlain, the '278 patent, and the '109 patent do not teach a mixture of Type I and Type IV collagen in a ratio of about 1:1 for supporting biological activity. According to the Office Action, Humes does teach the use of Type I and Type IV collagen in about 1:1 ratios to support biological activity (column 3, lines 65-66). In the opinion expressed in the Office Action, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ Humes' ratio of about 1:l of Type I and Type IV collagen because the other references do not quantitatively teach specific ratios between Type I and Type IV collagen for the desired aim of supporting biological activity. The Office Action asserted that Chamberlain provides additional motivation by teaching that collagen tubes have multiple advantages over silicone tubes, but that "the required characteristics of a nerve guide remain to be fully delineated" (page 1401). The Office Action further stated that while porous collagen tubes permit diffusion of nutrients and growth-promoting factors from the external

environment to the injured nerves in order to promote nerve regeneration (an observation the Office Action asserted is supported by two studies according to Chamberlain), if the tube is too porous, important wound-derived neurotrophic factors may be allowed to exit the injury site prematurely through the tube. The Office Action further stated that Chamberlain reports that his own study has shown that the most favorable results were obtained with a non-porous collagen tube filled with a CG copolymer because said tube facilitated the retention of the endogenous neurotrophic factors in the nerve injury gap site while allowing for the infiltration of smaller molecular weight nutrients through the tube. The Office Action stated that Chamberlain concludes "additional experimentation with porous and non-porous collagen tubes that differ in permeability may be used to address this issue" (page 1402), which, in the opinion expressed in the Office Action, is a suggestion by the primary reference to try to optimize the ratio of Type I and Type IV collagen for the known and motivating purpose of improving the therapeutic results. The Office Action thus concluded that the artisan would be motivated to look to the Humes reference to supply this missing information if said artisan was actually going to reduce to practice a combination of Type I and Type IV collagen because such information would be required during fabrication and use of the neural regeneration tube.

The Office Action further stated that Applicant's arguments filed August 5, 2010 have been fully considered but were not found persuasive because "Humes is not needed to overcome the asserted deficiencies of the previous rejections and is improperly argued in isolation from the other references." The Office Action further states that in response to Applicant's argument that Humes is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the

claimed invention. (citations omitted). In this case, the Office Action argues, Humes is in the field of cellular biology and the growth of cells, which is analogous to the other combined references.

In response, Applicants respectfully traverse the rejection. Applicants first refer to the comments presented above in connection with the obviousness rejection based on Chamberlain, the '278 patent and the '109 patent. The further cited Humes reference does nothing to overcome the nonobviousness of the claims based on the unexpected results noted above, nor does it provide any other reason to suggest the claims are obvious over the presently cited art. Humes does not even relate to nerve regeneration tubes, but instead is directed toward a renal tubule tissue system wherein adult kidney cells are cultured in a medium which may contain Type I collagen and/or Type IV collagen. Humes therefore cannot be combined with the other applied references to render obvious, or make predictable, the unexpected results achieved with the present invention. Therefore, for at least the reasons reiterated above, the invention is not obvious over the combination of reference teachings suggested in the Office Action. Accordingly, Applicants respectfully request reconsideration and withdrawal of the above obviousness rejection.

In view of the above remarks presented herein and those already of record, Applicants believe all of the concerns set forth in the October 7, 2010 Final Office Action have been fully overcome and the application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite such allowance or otherwise advance prosecution in the case.

Respectfully submitted,

October 7, 2011 By _____

Patrick T. Skacel
Reg. No. 47,948
Attorney for Applicants
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
Suite 800, 1425 K Street, N.W.
Washington, D.C. 20005
Telephone: (202)783-6040

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